VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Epidemiology of skeletal related events

Metastases to bone are common in patients with advanced malignancies, particularly in patients with breast, prostate, lung, kidney, and bladder cancer. In cancer therapy, the clinical impact of progressive bone cancer is observed by a composite end point termed skeletal-related events (SRE), which encompasses spinal cord compression, fracture caused by a disease that led to weakness (pathological fracture), a need for external beam radiation or surgery to bone, and hypercalcaemia of malignancy. In a retrospective review seventy-eight percent of patients (192 of 245) either presented with or developed at least one SRE after the diagnosis of metastatic bone disease. Related events (RE) were frequently multiple; 39% (74 of 192) sustained three or more discrete SRE[1].

Patients at risk of bone loss include smokers, those with excessive alcohol use, low calcium intake, sedentary lifestyle, and men with diminished functional activity of the gonads (testes). Osteoporosis affects approximately 75 million people in Europe, the United States, and Japan. The more common human cancers spreading to bone are breast, prostate, multiple myeloma, and kidney. The incidence of multiple myeloma in the United States is estimated at 15,000 annually, and these malignant plasma cells usually attack bone structure causing degenerative bone (bone cell death/damage) lesions. Bone is the most common site for breast cancer related distant disease recurrence and it is estimated to affect up to 75% of women with advanced breast cancer. Of those affected with bone metastasis, two- thirds will develop a SRE. The median survival with advanced breast cancer is about 18–26 months after diagnosis of bone metastasis, placing women at risk of skeletal complications. Approximately one-third of patients with advanced renal cell carcinoma develop bone metastases. However once this occurs the 2-year survival rate decreases to 10%–20% with a median survival of 1 year. The natural history of untreated patients with prostate cancer and bone metastases show that almost 50% had experienced at least one SRE by 2 years, the majority of which comprised a pathologic fracture(s) or need for palliative radiation. Greater than 80% of men dying of prostate cancer have autopsy- proven bone metastases[2]

In a population-based cohort study in Denmark it was concluded that among breast cancer patients with bone metastases, there was a strong tendency towards development of
SREs within a year of bone metastases diagnosis; however, this phenomenon stabilized beyond 5 years of bone metastases diagnosis[3].

Epidemiology of Tumour-Induced Hypercalcaemia

Tumor induced increase calcium levels (TIH) is the second most common consequence of cancer following cancer associated cachexia syndrome(CACS) which is characterized by loss of weight, muscle atrophy and weakness. TIH is essentially due to a marked increase in bone cell

(osteoclast) mediated resorption. Parathyroid- hormone-related protein (PTH-rp) also plays an essential role in causing TIH. TIH is considered as an emergency situation because of the often-severe symptoms. Dehydration, renal failure, mental confusion, nausea, vomiting, anorexia and ECG abnormalities may evolve rapidly with increasing levels of serum calcium. TIH is seen in many types of malignancies with or without bone metastases. The incidence of TIH amongst advanced malignancies is reported to be 5-20%.

Generally, the underlying disease is incurable however; treatment of TIH may improve quality of life. Symptoms related to the Central Nervous System (CNS) and to intravascular volume depletion can be controlled with effective anti-hypercalcemia therapy in more than 70% of cases. Serum calcium levels also decrease to within normal limits in about 40-80% of cases. TIH occurs most commonly secondary to cancers of breast, lungs, prostate and myeloma[4].

Epidemiology of Osteoporosis

Osteoporosis is characterized by reduced bone mass and disruption of bone architecture, resulting in increased risk of fragility fractures which represent the main clinical consequence of the disease. Fragility fractures are associated with substantial pain and suffering, disability and even death for affected patients and substantial costs to society. The most common osteoporotic fractures are those at the hip, spine, forearm and humerus. At the age of 50 years, the remaining lifetime probability of one of these fractures is 22 % and 46 % in men and women, respectively. Osteoporosis causes more than 8.9 million fractures annually worldwide and in Europe osteoporotic fractures account for 2 million disability adjusted life years (DALYs) annually, somewhat more than are accounted for by hypertensive heart disease or rheumatoid arthritis. In a report from 2010 twenty-two million women and 5.5 million men were estimated to have osteoporosis in Europe. The number of osteoporotic fractures is rising in many countries and the easons for this relate in part to the increased longevity of the population.[5]

Epidemiology of Paget's disease

Paget's disease of bone (PDB) is also known as osteitis deformans. Paget's disease is a common focal skeletal disorder that may involve a single bone or multiple bones.Although many PDB patients are asymptomatic, significant symptoms including bone pain, bone deformity, secondary arthritis, and neurologic problems occur in some patients. PDB is the second most common bone remodeling disease after osteoporosis. This condition occurs in 1–2% of white adults older than 55 years. The prevalence of PDB increases with age and is slightly more common in men. First-degree relatives of patients with PDB have an increased risk of PDB. Familial PDB also tends to be diagnosed at a younger age and involve more of the skeleton than sporadic disease. Genetic and environmental factors are important in the development of this disease.[6]
The prevalence differs amongst various ethnic/geographic groups. This disease is most common in the United Kingdom and Western Europe but is also common in British immigrants to Australia, New Zealand, South Africa, and South America. The disease is uncommon in African blacks, Scandinavia, China, Japan, Southeast Asia, and the Indian subcontinent.

VI.2.2 Summary of treatment benefits

Zoledronic acid belongs to the class of drugs called bisphosphonates and acts primarily on bone by inhibiting osteoclast-mediated bone resorption. It therefore stops the action of the osteoclasts, the cells in the body that are involved in breaking down the bone tissue. This leads to less bone loss. The reduction of bone loss helps to make bones less likely to break, which is useful in preventing fractures in patients with bone metastases and patients with osteoporosis. Patients with tumors can have high levels of calcium in their blood, released from the bones. By preventing the breakdown of bones, zoledronic acid also helps to reduce the amount of calcium released into the blood.

Zoledronic acid SUN is available as solution for infusion (drip) into a vein in different concentration and formulation (e.g. 4mg/5ml concentrate for solution for infusion and 5mg/100 ml solution for infusion). Zoledronic acid SUN is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorized in the European Union (EU) called Zometa/Aclasta

Since Zoledronic acid SUN is a 'generic medicine' its benefits and risks are taken as being the same as the reference medicinal product.

The safety and efficacy profile of Zoledronic acid has been demonstrated in several clinical trials in cancer patients with bone metastases, in patients with tumor induced hypercalcemia and also in patients with osteoporosis (e.g. post-menopausal women, osteoporosis associated with long-term systemic glucocorticoid therapy) details of these studies can be found in the EPAR of the reference medicinal product Zometa/Aclasta and also in section 5.1 of SmPC.[7-10]

VI.2.3 Unknowns relating to treatment benefits

Very limited information is available regarding treatment benefits of zoledronic acid in paediatric patients, pregnant and breastfeeding women. There are no adequate and well controlled studies in patients with hepatic insufficiency and severe renal impairment and also in other races than Caucasian.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
1. Impaired kidney function [Renal function impairment]	Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products.	Serum creatinine levels should be assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, the zoledronic acid should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. Renal function monitoring and avoidance of drugs like aminoglycosides, NSAIDS and thalidomide. The use of zoledronic acid is not recommended in patients with severe renal impairment.

Risk	What is known	Preventability
2. Bone damage in the jaw [Osteonecrosis of the jaw (ONJ)]	Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates (class of medicines to which zoledronic acid belongs). Risk factors involved in developing ONJ are: • potency of the bisphosphonate, higher risk for parenteral administration and cumulative dose. • cancer, chemotherapy, radiotherapy • corticosteroids use • smoking • poor oral hygiene • history of dental disease, periodontal disease, invasive dental procedures and poorly fitting dentures.	Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/ risk assessment. Preventive dental exams should be performed before starting zoledronic acid SUN. Improved oral hygiene and any required dental surgery before dosing with Zoledronic acid. Avoid invasive dental procedures during therapy.
3. Atypical fractures of the femur [Atypical fractures of the femur]	Atypical (subtrochanteric and diaphyseal) femoral fractures have been reported with bisphosphonates, primarily in patients receiving long-term treatment for osteoporosis. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Poor healing of these fractures has also been reported.	Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture, Evaluation of patients with thigh, hip or groin pain to rule out an atypical femoral fracture should be carried out.

Risk	What is known	Preventability
4. Eyes disorders [Ocular adverse events]	Several side*effects have been associated with bisphosphonate class. Ocular hyperaemia (redness of the eye), eye pain, and inflammation of different parts of the eye such as conjunctivitis, uveitis, episcleritis, iritis scleritis and orbital inflammation have been reported with zolendronic acid use. Inflammation of parts of eyes may occur, usually within two weeks of the infusion and are transient in nature and subside with topical treatment.	Should not be used in patients with current or recent uveitis, or a history of bisphosphonate-associated uveitis. Treating physician and patient should monitor for early symptoms of ocular adverse events (such as pain, swelling, itching and redness of the eye).
5. Low calcium levels in the blood [Hypocalcaemia]	Soon after infusion of zoledronic acid, blood calcium levels are seen to decrease in some patients. Cardiac arrhythmias and neurologic adverse events (including seizures, numbness and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalization have been reported. In some instances, the hypocalcaemia may be life-threatening.	Calcium and Vitamin D supplements before and after infusion. Standard hypercalcaemia- related metabolic parameters, such as serum levels of calcium, phosphate and magnesium should be carefully monitored after initiating zoledronate therapy, in case of such events, short-term supplemental therapy may be necessary. Appropriate physical activity, non-smoking and healthy diet is advised for proper bone health. Patients should be informed about symptoms of hypocalcaemia (such as loss of sensation in finger tips, muscle cramps) and receive adequate clinical monitoring during the period of risk.

Risk	What is known	Preventability
6. Post-dose reaction [Acute Phase Reaction]	Post-dose symptoms like fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea and arthralgia occur within first three days after the infusion. These are mostly mild to moderate in severity and self- limiting.	Standard oral dose of an analgesic at the time of infusion and repeated up to 72 hours if required.
7. Severe allergic reaction [Anaphylaxis]	Hypersensitivity (allergic) reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported.	Contraindicated in the patients having hypersensitivity to zoledronic acid or to any other product's excipients or to any bisphosphonates. The risk of hypersensitivity associated with the use of medicines can be managed by monitoring of symptoms and signs patients and usual precautions related to hypersensitivity.
8. **Irregular and often abnormally fast heart rate** [Atrial Fibrillation]	In a controlled clinical trial the overall incidence of atrial fibrillation was 2.5% and 1.9%was seen in patients receiving zoledronic acid g and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% and 0.6% in patients receiving Zoledronic acid and placebo, respectively. The onset of atrial fibrillation might be related to events occurring secondary to intravenous bisphosphonate administration, such as transient hypocalcaemia or increased proinflammatory cytokine release, which manifest as so-called post-dose symptoms, seen in a proportion of patients mainly after intravenous bisphosphonate administration	It is not always possible to predict such side effect after infusion of Zoledronic acid. However, if the patient present abnormal heart rate (e.g. palpitation) during infusion or later one, the doctor may decide to perform an EKG and to stop treatment with Zoledronic acid.

Important Potential Risks

Risk	What is known(including reason why it is considered a potential risk)
9. Side effects affecting the circulatory system and the brain [Cerebrovascular adverse events]	Conflicting results on the increase of cerebrovascular adverse effects associated with bisphosphonate use have been reported in different studies, but there is not enough evidence to say that zoledronic acid is associated with increased incidence of strokes.
10. Scar tissue in the filtering unit of the kidney [Focal glomerulosclerosis segmental glomerulosclerosis	Administration of bisphosphonate, especially by the intravenous route, carries a certain, well- established risk of deterioration of kidney function. Although toxic acute tubular necrosis (death of tubular epithelial cells that form the renal tubules of the kidneys) and focal segmental glomerulosclerosis (scarring in the kidney) have been implicated in the mechanism of kidney toxicity.
11. Bone damage in other location than the jaws [Osteonecrosis outside the jaw]	Osteonecrosis of the jaw is a well-known and dreaded complication after the administration of bisphosphonates. Recently a few cases of bisphosphonate-associated osteonecrosis of in other location than jaw such as the external ear canal have been described, especially after long-lasting bisphosphonate therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma.
12. Delayed union/non- union fractures [Fracture healing impairment]	Cases of delayed union/non- union fracture have been reported in clinical trials with zoledronic acid infusion (but incidence was not significantly different from placebo group).
13. Inflammation and scarring of the lungs [Interstitial lung disease]	In the post marketing surveillance cases of bronchospasmand interstitial lung disease with positive rechallenge have been reported with zoledronic acid.
14. Irregular heart rhythm [Cardiac Arrhythmia]	Cardiac arrhythmias and neurologic adverse events (including seizures, numbness and tetany) have been reported secondary to cases of severe hypocalcaemia.
15. Medication error [Medication error]	Due to the availability of various zoledronic acid containing medicines with similar names, but with different indications, strengths and dosing regimens (Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion vs. Zoledronic acid 5 mg solution for infusion) medication errors are possible.

Risk	What is known(including reason why it is considered a potential risk)
16. Interactions with medication that can significantly affect renal function [Potential interactions with nephrotoxic products]	Zoledronic acid is not broken down in the body and is eliminated via the kidneys. There is a possibility that concomitant use of drugs (e.g. aminoglycosides-a type of antibiotics or diuretics-water pills, that may cause dehydration) are injurious to kidneys and may increase the severity of impairment of kidney functions when used together with Zoledronic acid. In multiple myeloma patients, the risk of kidney dysfunction may be increased when zoledronic acid is used in combination with thalidomide.

Missing Information

Risk	What is known
17. Use by pregnant or breastfeeding women [Use in pregnancy/ lactation]	Zoledronic acid should not be used during pregnancy. There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity. The potential risk for humans is unknown. It is not known whether zoledronic acid is excreted into human breast milk. Zoledronic acid must not be used during pregnancy and in breast-feeding women.
18. Use in children **[**Use in paediatric population]	Lack of data on safety and efficacy in children and adolescents below 17 years of age.
19. Use in patient with liver impairment **[**Use in patients with hepatic insufficiency]	As only limited clinical data is available in patients with severe hepatic insufficiency, no specific recommendations can be given for this population.
20. Use in patient with severe kidney function damage **[**Un in patients with severe renal impairment]	Due to the potential impact of zoledronic acid on kidney function, and lack of clinical safety data in patients with severe kidney insufficiency, the use of zoledronic acid is not recommended in patients with severe kidney insufficiency
21. Races other than Caucasian [Races other than Caucasian]	The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases, but there are insufficient data available regarding the use of Zoledronic acid in races other than Caucasian.

VI.2.5 Summary of risk minimisation activities by safety concern

Summary of Product Characteristics (SmPC) of Zoledronic acid SUN 4 mg /5ml concentrate for solution for infusion and Zoledronic acid SUN 5 mg/100ml solution for infusion provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL) for patients.

For all above mentioned risk the routine risk minimisation measures are given in SUN's SmPCs and PLs of Zoledronic acid. These medicines have also special conditions for its safe and effective use called **additional risk minimisation measure** for ***identified risk of osteonecrosis of the jaw.*** It consists in suppling of educational material in the form of **Patient Reminder Card** (for Zoledronic acid SUN 5 mg/100ml and Zoledronic acid SUN 4 mg /5ml).

Another **additional risk minimisation measure** for *identified risk of renal function impairment* it consists in suppling of educational material in the form of Doctor's Information Guide and Patient's Information Guide for the product Zoledronic acid SUN 5mg/100ml.

The key elements of this additional risk minimisation measure which address the following safety concerns: ***osteonecrosis of the jaw and renal function impairment*** are presented in the table below with cross-reference to Patient Reminder Card, Doctor's Information Guide and Patient Information Guideincluded as mock-up example in Annex 11.

Safety concern – Bone damage in the jaw (Osteonecrosis of jaw)

Risk minimisation measure(s)- Patient education
Objective and rationale: Patients to understand the risk of bone damage in the jaw and the need of regular dental check-ups and good oral hygiene.
Main additional risk minimisation measure: The following educational material will be distributed (see mock example in Annex 11): • **Patient Reminder Card** specifically aimed at facilitating patient's awareness on the risk of bone damage in the jaw (Osteonecrosis of jaw –ONJ) will be supplied with the product. The Patient Reminder Card provides detailed information to the patient regarding: • symptoms of ONJ and the importance of contacting their dentist if any problems with the mouth or teeth occurred before /during treatment with Zoledronic acid or other bisphophonates. • risk factors for ONJ such as: teeth and gum diseases, tooth extractions, cancer, smoking, steroids and cancer treatment, poor hygiene, prior bisphophonates therapy. • need of routine dental check-ups and proper oral hygiene.

Safety concern-Impaired kidney function (Renal function impairment)

Risk minimisation measure(s)- Healthcare Professional and patient education
Objective and rationale: To remind HCP and patients how the medicine should be used, to explain the medicine's side effects including to understand the risk of impaired kidney function and how can be this risk minimized.

Risk minimisation measure(s)- Healthcare Professional and patient education
Main additional risk minimisation measure: The following educational material will be distributed (see mock example in Annex 11): • **Doctor's Information Guide** • **Patient Information Guide** The Doctor's Information Guide provides detailed information to the healthcare professional regarding: • Indications • Administration • Contraindications • Precautions for use • Recommendations • Side effects • Reporting of suspected adverse reactions The Patient's Information Guide provides detailed information to the patients regarding: • What is Zoledronic acid 5 mg? • How does Zoledronic acid 5 mg work? • How is Zoledronic acid 5 mg administered? • How frequently is administered Zoledronic acid 5 mg infusion? • What should tell the patients to their doctors before administration of Zoledronic acid 5 mg? • Which patients should not receive Zoledronic acid 5 mg? • What patients need to know before administration of Zoledronic acid 5 mg? • Important side effects of Zoledronic acid 5 mg • Reporting of side effects • Other measures that patients can take

VI.2.6 Planned post-authorization development plan

None.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
1.0	April 2012	**Important potential risk:** • Atypical femoral fracture	An abbreviate core RMP was approved within NL/H/2336/001/DC for Zoledronic acid SUN 4 mg /5 ml concentrate for solution for infusion.
1.0	November 2012	**Important potential risk:** Atypical femoral fracture	Only abbreviate core RMP was approved within NL/H/2646/001/DC Zoledronic acid SUN 5 mg /100 ml solution for infusion

Version	Date	Safety Concerns	Comment
1.1	03 Jul 2014	**Important identified risks:** 1. Renal function impairment: 2. Osteonecrosis of the jaw (ONJ) 3. Atypical fractures of the femur 4. Ocular adverse events 5. Hypocalcaemia 6. Acute Phase Reaction 7. Anaphylaxis ***Important potential risks*** 8. Cerebrovascular accident (stroke) 9. Focal segmental glomerulosclerosis 10. Fracture healing impairment 11. Interstitial lung disease 12. Cardiac arrhythmias: 13. Potential interactions with products that can significantly affect renal function ***Missing information*** 14. Use in pregnancy/lactation 15. Use in paediatric population 16. Use in patients with hepatic insufficiency 17. Patients with severe renal impairment	Vs 1.1 approved for Zoledronic Acid SUN 4mg/100 ml solution for infusion within NL/H/3103-001/DC
2.0	16-Jul-15	**Important identified risks:** 1. Renal function impairment: 2. Osteonecrosis (death of bone tissue)of the jaw (ONJ) 3. Atypical fractures of the femur 4. Ocular adverse events 5. Hypocalcaemia 6. Acute Phase Reaction 7. Anaphylaxis ***Important potential risks*** 8. Cerebrovascular accident (stroke) Focal segmental glomerulosclerosis 9. Osteonecrosis outside the jaw and nonunion or delayed union fractures 10. Interstitial lung disease 11. Irregular heart rhythm (including Atrial Fibrillation) 12. Medication errors	Submitted within renewal of Zoledronic acid 4mg/5ml solution for infusion (Procedure no: NL/H/2336/001/R/001)

Version	Date	Safety Concerns	Comment
		13. Potential interactions with products that can significantly affect renal function ***Missing information*** 14. Use in pregnancy/lactation 15. Use in paediatric population 16. Use in patients with hepatic insufficiency 17. Patients with severe renal impairment	
2.1	12-Nov-15	**Important identified risks:** 1. Renal function impairment 2. Osteonecrosis (ONJ) 3. Atypical fractures of the femur 4. Ocular adverse events 5. Hypocalcaemia 6. Acute Phase Reaction *7.* Anaphylaxis *8.* Atrial Fibrillation ***Important potential risks*** 9. Cerebrovascular adverse events 10. Focal segmental glomerulosclerosis 11. Osteonecrosis outside the jaw 12. Fracture healing impairment 13. Interstitial lung disease 14. Cardiac arrhythmias 15. Medication error 16. Potential interactions with nephrotoxic medication ***Missing information*** 17. Use in pregnancy/lactation 18. Use in paediatric population 19. Use in patients with hepatic insufficiency 20. Use in patients with severe renal	Following recommendations of RMS (NL) from Preliminary Renewal Assessment Report (Procedure no: NL/H/2336/001/R/001) the summary of safety concerns was updated as follows: • the important identified risk *"Atrial Fibrillation"* was added and potential risk *"Irregular heart rhythm (including Atrial Fibrillation)"* was amended to *"Cardiac arrhythmias"*. • two potential risks were included *"Osteonecrosis outside the jaw"* and *"Fracture healing impairment"* instead of previous potential risk *"Osteonecrosis outside the jaw and non-union or delayed union fractures*" "*Races other than Caucasian"* was added as missing informatio

Version	Date	Safety Concerns	Comment
		impairment 21. Races other than Caucasian	
		Part I and III, Part V, and Part VI were amended. **Annex 2, 7, 11 and 12 were updated.**	Formatting of RMP was changed as per new template released by EMA (Guidance on format of the risk management plan (RMP) in the EU. In order to harmonized the RMP with all available Zoledronic acid strengths/formulation in EEA ,the RMP vs 2.1 was also updated to include information on other SUN Zoledronic acid containing products. This vs was planned to be submitted also via type II variation within following DCP procedures: NL/H/2646/001/DC] and NL/H/3103/001/DC. Part III table III.1, Part V and Part VI were updated in line with changes performed in the Summary of safety concerns. In Part III was redrafted to included information on routine PhV activities including details on performing targeted follow-ups for following risks: *ocular adverse events, atrial fibrillation, cardiac arrhythmias, cerebrovascular AEs, osteonecrosis of the jaw, renal function impairment, atypical femoral fractures.* The questionnaires for targeted follow-up as mentioned in Part III were also added in Annex 7. In Part V a Patient Reminder Card as additional risk minimisation measure for osteonecrosis of the jaws was proposed. The mock-up of Patient reminder card was also included in Annex 11. Part VI was redrafted and information on epidemiology of osteoporosis and Paget's diseases were added Information on additional RMM- Patient Reminder

Version	Date	Safety Concerns	Comment
			Card for ONJ was also included. Updated SmPC and PL for all SUN Zoledronic acid containing products were included in Annex 2. Annex 12 was changed to included only relevant citation references.
3.0	21-Jul-16	**Same safety concerns as in approved vs 2.1**	The common RMP for SUN Pharma Zoledronic acid containing products approved within renewal of NL/H/2336/001/DC was updated to remove information related to Zoledronic acid SUN 4 mg/100 ml solution for infusion as MAs within NL/H/3103/001/DC are being withdrawn. Annex 2 was updated with SmPC and PL for Zoledronic acid SUN 4 mg /5 ml concentrate for solution for infusion and 5 mg/100ml solution for infusion.
4.0	06-Sep-17	**Same safety concerns as in approved vs 3.0**	New additional risk minimisation measure for the safety concern- Renal function impairment in the form of educational materials: Doctor's Information Guide, Patient's Information Guide.This apply for the product Zoledronic acid 5mg SUN. In the Final Assessment Report of the DCP for Zoledronic acid 5 mg the requirement of the RMS was to provide these educational materials. Results of Annual cumulative review will be presented in periodic safety reports (e.g ADCO, SERs).
5.0	18-Jan-18	**Same safety concerns as in approved vs 4.0**	Effectiveness of the risk minimisation measures have been added for every safety concern.
5.1	20-Apr-18	**Same safety concerns as in approved vs 4.0**	As a response to preliminary variation assessment Report, effectiveness of the risk minimisation measures were amended and following subsectionswere

Version	Date	Safety Concerns	Comment
			added for every safety concern: • How effectiveness of the risk minimisation measures for the safety concern will be measured. • Criteria for judging the success of the proposed risk minimisation measures. • Planned dates for assessment.